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APPLICATION NUMBER	FILING DATE	FIRST NAMED APPLICANT	ATTY. DOCKET NO.
09/016,061	01/30/98	HUSE	W P-IX2965

EXAMINER

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HM22/0410

ART UNIT	PAPER NUMBER
1644	21

DATE MAILED: 04/10/01

This is a communication from the examiner in charge of your application.
COMMISSIONER OF PATENTS AND TRADEMARKS

OFFICE ACTION SUMMARY

☑ Responsive to communication(s) filed on 1/22/01

☑ This action is **FINAL**.

☐ Since this application is in condition for allowance except for formal matters, **prosecution as to the merits is closed** in accordance with the practice under *Ex parte Quayle*, 1935 D.C. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire 3 month(s), or thirty days, whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

Disposition of Claims

☑ Claim(s) ~~Being~~ 56-104 is/are pending in the application.
Of the above, claim(s) 60,61,63,64,69,78-83,92,93,98-104 is/are withdrawn from consideration.
☐ Claim(s) _____ is/are allowed.
☑ Claim(s) 55-59,62,65-68,70-77,84,85,90,91,94-97 is/are rejected.
☐ Claim(s) _____ is/are objected to.
☐ Claim(s) _____ are subject to restriction or election requirement.

Application Papers

☐ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.
☐ The drawing(s) filed on _____ is/are objected to by the Examiner.
☐ The proposed drawing correction, filed on _____ is ☐ approved ☐ disapproved.
☐ The specification is objected to by the Examiner.
☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

☐ All ☐ Some* ☐ None of the CERTIFIED copies of the priority documents have been

☐ received.
☐ received in Application No. (Series Code/Serial Number) _____.
☐ received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____

☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

☐ Notice of Reference Cited, PTO-892
☑ Information Disclosure Statement(s), PTO-1449, Paper No(s). _____
☐ Interview Summary, PTO-413
☒ Notice of Draftperson's Patent Drawing Review, PTO-948
☐ Notice of Informal Patent Application, PTO-152

--SEE OFFICE ACTION ON THE FOLLOWING PAGES--

DETAILED ACTION

1. Applicant's amendment, filed 1/22/01 (Paper No. 20), is acknowledged.
Claims 56 and 74 have been amended.

Claims 1-55 have been canceled have been canceled previously.
Claims 56-104 are pending

Claims 56-59, 62, 65-68, 70-77, 84, 85, 90, 91 and 94-97 are under consideration in the instant application; as they read on the elected species.

Claims 60, 61, 63, 64, 69, 78-83, 92, 93 and 98-104 have been withdrawn from consideration by the examiner 37 CFR 1.142(b), as being drawn to a nonelected invention and/or species.

2. With respect to the restriction requirement and applicant's comments about undue burden (see Paper No. 20, filed 1/22/01 and Paper No. 10, filed 9/13/99); the MPEP 803 (July 1998) states that "For purposes of the initial requirement, a serious burden on the examiner may be prima facie shown if the examiner shows by appropriate explanation either separate classification, separate status in the art, or a different field of search". The Restriction Requirement enunciated in the previous Office Action meets this criterion and therefore establishes that serious burden is placed on the examiner by the examination Groups. The Inventions are distinct for reasons elaborated in set forth in Paper Nos. 6 and 11.

3. Applicant's disclaimer of priority to USSN 08/79,391, filed 1/30/97, and statement that the priority date of the present application is the actual filing date, 1/30/98 is acknowledged.

4. In view of applicant's Petition to Correct Inventorship Under 37 CFR 1.48(b), filed 1/22/01 (Paper No. 19); the inventorship in this nonprovisional application has been changed by the deletion of Scott Glaser.
The inventor of the instant application is William Huse.

5. The text of those sections of Title 35 USC not included in this Action can be found in a prior Action.
This Office Action will be in response to applicant's arguments, filed 1/22/01 (Paper No. 20).
The rejections of record can be found in the previous Office Action (Paper No. 16).

6. Formal drawings and photographs have been submitted which fail to comply with 37 CFR 1.84.
Please see the enclosed form PTO-948.

7. Claims 56-59, 62, 65-68, 70-77, 84, 85, 90, 91 and 94-97 are rejected under 35 U.S.C. § 112, first paragraph, as the specification does not contain a written description of the claimed invention, in that the disclosure does not reasonably convey to one skilled in the relevant art that the inventor(s) had possession of the claimed invention at the time the application was filed.

The specification as originally filed does not provide support for the invention as now claimed: "one or more CDR's having".

Applicant's amendment, filed 1/22/01 (Paper No. 20), directs support to page 6, lines 1-10, and page 16, lines 10-17 of the specification and Figure 2 for the written description for the above-mentioned "limitation".

However, the specification as filed does not provide a written description of this phrase, including a range of "one or more CDRs having". The specification does not provide sufficient blazemarks nor direction for the instant products encompassing the above-mentioned "limitation"; as it is currently recited. The instant claims now recite limitations which were not clearly disclosed in the specification as-filed, and now change the scope of the instant disclosure as-filed. It cannot be said that a subgenus is necessarily described by a genus encompassing it and a species upon which it reads. In re Smith 173 USPQ 679, 683 (CCPA 1972). See MPEP 2163.05(b). Such limitations recited in the present claims, which did not appear in the specification, as filed, introduce new concepts and violate the description requirement of the first paragraph of 35 U.S.C. 112.

Applicant is required to cancel the new matter in the response to this Office action

Alternatively, applicant is invited to provide sufficient written support for the "limitation" indicated above. See MPEP 714.02 and 2163.06

8. Claims 56-59, 62, 65-68, 70-77, 84, 85, 90, 91 and 94-97:

It is apparent that the LM609 antibody is required to practice the claimed invention. As a required element, it must be known and readily available to the public or obtainable by a repeatable method set forth in the specification. If it is not so obtainable or available, the enablement requirements of 35 USC 112, first paragraph, may be satisfied by a deposit of the hybridoma which produces this antibody. See 37 CFR 1.801-1.809.

In addition to the conditions under the Budapest Treaty, applicant is required to satisfy that all restrictions imposed by the depositor on the availability to the public of the deposited material will be irrevocably removed upon the granting of a patent in U.S. patent applications.

Amendment of the specification to recite the date of deposit and the complete name and address of the depository is required. As an additional means for completing the record, applicant may submit a copy of the contract with the depository for deposit and maintenance of each deposit.

If the original deposit is made after the effective filing date of an application for patent, the applicant should promptly submit a verified statement from a person in a position to corroborate the fact, and should state, that the biological material which is deposited is a biological material specifically identified in the application as filed, except if the person is an attorney or agent registered to practice before the Office, in which the case the statement need not be verified. See MPEP 1.804(b).

Applicant's arguments, filed 1/22/01 (Paper No. 20), have been fully considered but are not found convincing essentially for the reasons set forth previously in Paper No. 16.

Applicant's reliance on the nucleotide and amino acid sequences of the LM609 variable regions is acknowledged.

As pointed out previously, it was noted that if the claimed and disclosed amino acid sequences or nucleic acid sequences set forth in the instant application encode the entire LM609 antibody, then a deposit for said LM609 antibody (hybridoma) is not required. The sequence of an entire immunoglobulin satisfies the biological deposit of said immunoglobulin.

Therefore, applicant's reliance on the variable regions of LM609 do not satisfy the enablement or deposit requirement for biological materials; given that these sequences do not provide for the entire structure of the LM609 immunoglobulin.

Applicant's arguments are not found persuasive.

9. Upon reconsideration of applicant's amended claims and arguments, filed 1/22/01 (Paper No. 20), have obviated the previous rejection under 35 U.S.C. § 112, first paragraph, with respect to the recitation of ""enhanced LM609 grafted antibody"; given that the skilled artisan would be able to screen for certain binding and functional properties of LM609 grafted antibodies.

10. Claims 56-59, 62, 65-68, 70-77, 84, 85, 90, 91 and 94-97 are rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

A) Claims 56-59, 62, 65-68, 70-77, 84, 85, 90, 91 and 94-97 are indefinite in the in the recitation of ""enhanced LM609 grafted antibody" because this phrase is relative in nature, which renders the claim indefinite. For example, pages 16-17, overlapping paragraph of the instant specification discloses that the functional characteristic of the antibody has been altered or augmented compared to a reference antibody, which can include both higher or lower affinity. Therefore, the claimed "enhanced LM609 antibody" can have contrasting properties and still be considered enhanced with respect to the referenced LM609 antibody. Further, the terms are not defined by the claims, the specification does not provide a standard for ascertaining the requisite degree, and one of ordinary skill in the art would not be reasonably apprised of the metes and bounds of the invention

Applicant's amended claims and arguments, filed 1/22/01 (Paper No. 20), have been fully considered but are not found convincing essentially for the reasons set forth previously in Paper No. 16.

The claims now recite certain functional properties such as "having integrin αvβ3 binding activity, integrin αvβ3-inhibitory activity", wherein the αvβ3 binding affinity of said enhanced LM609 grafted antibody is maintained.

Applicant argues that the term "enhanced" is one in which a functional characteristic of the antibody has been altered or augmented compared to a reference antibody so that the antibody exhibits a desirable property or activity (page 16, line 30, to page 17, line 14).

Applicant acknowledges that the exemplary enhanced activity includes higher or lower affinity, increased or decreased association or dissociation rates or increased stability compared to a reference antibody.

In contrast to applicant's assertions and for the reasons of record and reiterated herein; the claimed "enhanced LM609 antibody" can have contrasting properties and still be considered enhanced with respect to the referenced LM609 antibody. Further, the terms are not defined by the claims, the specification does not provide a standard for ascertaining the requisite degree, and one of ordinary skill in the art would not be reasonably apprised of the metes and bounds of the invention

Applicant's arguments are not found persuasive.

For examination purposes and as applicant acknowledges; it appears that all that is required of the "enhanced" LM609 antibody is that the activity of the enhanced LM609 grafted antibody is maintained.

B) Claims 56-59, 62, 65-68, 70-77, 84, 85, 90, 91 and 94-97 are indefinite in the recitation of "LM609" because its characteristics are not known. The use of "LM609" monoclonal antibody as the sole means of identifying the claimed antibody renders the claim indefinite because "LM609" is merely a laboratory designation which does not clearly define the claimed product, since different laboratories may use the same laboratory designation to define completely distinct cell lines or hybridomas.

Applicant's arguments, filed 1/22/01 (Paper No. 20), have been fully considered but are not found convincing essentially for the reasons set forth previously in Paper No. 16.

Applicant's reliance on the nucleotide and amino acid sequences of the LM609 variable regions is acknowledged.

As pointed out previously and above; it was noted that if the claimed and disclosed amino acid sequences or nucleic acid sequences set forth in the instant application encode the entire LM609 antibody, then a deposit for said LM609 antibody (hybridoma) is not required. The sequence of an entire immunoglobulin satisfies the biological deposit of said immunoglobulin.

Therefore, applicant's reliance on the variable regions of LM609 do not satisfy defining the biological

material LM609; given that these sequences do not provide for the entire structure of the LM609 immunoglobulin.

Applicant's arguments are not found persuasive.

C) The amendments must be supported by the specification so as not to add any new matter. See MPEP 714.02 and 2163.06

11. Claims 56-59, 62, 65-68, 70-75, 77, 84, 85, 90, 91 and 94-97 are rejected under 35 U.S.C. § 102(e) as being anticipated by Brooks et al. (U.S. Patent No. 5,753,230; 1449) for the reasons of record set forth in Paper No. 16.

Applicant's arguments, filed 1/22/01 (Paper No. 20), have been fully considered but are not found convincing essentially for the reasons set forth previously in Paper No. 16.

Applicant submits that the instant enhanced antibodies are novel over the antibodies of Brooks et al. ; since that Brooks et al. does not teach an enhanced LM609 grafted antibody comprising one or more CDRs having a least one amino acid substitution in one or more CDRs of a LM609 grafted heavy chain variable region polypeptide, including SEQ ID NOS: 6 and 8.

As pointed out; for examination purposes and as applicant acknowledges; it appears that all that is required of the "enhanced" LM609 antibody is that the activity of the enhanced LM609 grafted antibody is maintained.

Therefore, the claimed "enhanced LM609 antibody" can have contrasting properties and still be considered enhanced with respect to the referenced LM609 antibody.

Given the prior art teaching of humanized LM609 antibodies and that the claimed recitation of "enhanced LM609 antibody" encompasses a variety of modified forms of the LM609, provided it differs from the native LM609 antibody; the prior art humanized antibodies read on the claimed antibodies.

Applicant is reminded that no more of the reference is required than that it sets forth the substance of the invention. The prior art and the instant claims rely upon the same LM609 antibody.

The claimed functional limitations would be inherent properties of the referenced LM609 antibodies and humanized antibodies thereof.

Applicant's arguments are not found persuasive and the rejection is maintained.

12. Claims 56-59, 62, 66-68, 70, 71, 74-76, are rejected under 35 U.S.C. § 103(a) as being unpatentable over Brooks et al. (U.S. Patent No. 5,753,230; 1449) in view of art known gene cloning and expression strategies for deriving recombinant antibodies and fragments thereof, as disclosed on pages 10-39 or Examples I and II of the instant specification or as cited by references on the 1449, including Queen et al. (5,585,089), Rosok et al. (J. Biol. Chem. 271: 22611-2618, 1996), Glaser et al. J. Immunol. 149: 3903-3913, 1992) for the reasons set forth previously in Paper No. 16.

Applicant's arguments, filed 1/22/01 (Paper No. 20), have been fully considered but are not found convincing essentially for the reasons set forth previously in Paper No. 16.

Applicant submits that the instant enhanced antibodies are nonobvious over the antibodies of Brooks et al. alone or in combination of art known gene cloning and expression strategies for deriving recombinant antibodies and fragments thereof ; since that Brooks et al. does not teach an enhanced LM609 grafted antibody comprising one or more CDRs having a least one amino acid substitution in one or more CDRs of a LM609 grafted heavy chain variable region polypeptide, including SEQ ID NOS: 6 and 8.

Applicant asserts that any known art for gene cloning and expression strategies does not cure the deficiencies of Brooks et al.

As pointed out; for examination purposes and as applicant acknowledges; it appears that all that is required of the "enhanced" LM609 antibody is that the activity of the enhanced LM609 grafted antibody is maintained.

Therefore, the claimed "enhanced LM609 antibody" can have contrasting properties and still be considered enhanced with respect to the referenced LM609 antibody.

Given the prior art teaching of humanized LM609 antibodies and that the claimed recitation of "enhanced LM609 antibody" encompasses a variety of modified forms of the LM609, provided it differs from the native LM609 antibody; the prior art humanized LM609 antibodies in combination of art known gene cloning and expression strategies for deriving recombinant antibodies and fragments thereof read on the claimed antibodies.

As pointed out previously, with respect to specific amino acid changes including those which are encompassed by "enhanced LM609"; it would have been obvious given the teachings of humanized LM609 antibodies and art known methods to generate such humanized antibodies which retain the desired functional characteristics of the native antibody and to alter said antibody for therapeutic uses, including human therapy, as taught and known in the prior art.

Therefore the primary reference clearly teaches $\alpha v\beta 3$-specific antibodies the instant LM609 specificity and associated properties as valuable diagnostic and therapeutic tools in various biological processes. These references differ from the instant claims by not disclosing the generation of recombinant forms and nucleic acids of the LM609 antibody and hybridoma per se.

Given the availability of the LM609 antibody and hybridoma together with general immunoglobulin gene cloning and expression strategies, it would have been have been a matter of routine experimentation well within the ordinary skill level of art to generate chimeric or humanized LM609 antibodies, DNA encoding said antibodies. Given the highly conserved nature of immunoglobulin gene organization and structure and the availability of probes and PCR primers for immunoglobulin gene cloning, one of ordinary skill in the art could have isolated the functionally rearranged heavy and light chain variable regions from the LM609

hybridoma cell line and determined their sequences with a complete expectation of success. For example, the ordinary artisan does not need to determine the amino acid sequences of a rearranged V (variable) region before cloning.

The claims do not differ unexpectedly or unobviously from what one of ordinary skill in the art would have expected to obtain given the known LM609 hybridoma thereof, the known heavy and light chain and the art known techniques regarding the production of chimeric antibodies, as acknowledged by the number of available art known procedures disclosed in the instant specification and cited on the Information Disclosure Statement. For example. Queen et al. teaches the art known method of producing humanized antibodies of interest at the time the invention was made. Also, Rosok et al. and Glaser et al. teach providing for the selecting recombinant antibodies of interest, including selecting for alterations of antibody affinity.

Immunoglobulin gene structure and organization were well understood in the art a the time the claimed invention was made and that strategies for cloning the DNAs encoding immunoglobulin variable regions genes were well established in the art at the time the claimed invention was made, as were methods for the production of DNA constructs encoding immunoglobulin variable regions. In addition, it was known at the time the invention was made that the benefits of producing recombinant antibodies to reduce the immunogenicity of therapeutic and diagnostic antibodies in human patients. Also, the ordinary artisan would have selected for modified recombinant forms of the art known LM609, including those with modifications that would have provided for either lower immunogenicity or altered affinity to enhanced the diagnostic/therapeutic potential of the LM609 antibody specificity with an expectation of success at the time the invention was made. From the teachings of the references, it was apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention. Therefore, the invention as a whole was prima facie obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

Given the breadth of the claims to read on the LM609 antibody, the instant antibodies and nucleic acids read on a genus of antibodies (and nucleic acids) encompassed by LM609 and modifications thereof.

Applicant's arguments are not found persuasive and the rejection is maintained.

13. Claims 56-59, 62, 65-68, 70-77, 84, 85, 90, 91 and 94-97 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over (pending) claims 1-18 and 26-31 of copending application USSN 08/790,540 and (pending) claims 1-8, 15-26, 33-42 of copending USSN 08/791,391.

Although the conflicting claims are not identical, they are not patentably distinct from each other because each application is drawn to the same or nearly the same LM609-specific antibodies (and nucleic

acid) encoding said antibodies and modifications thereof.

The specific species recited in claims 65, 72, 73, 77, 84, 85, 90, 91, 94-97 which encompass specific amino SEQ ID NOS: 90 and 94 read as species on the genus of LM609-specific recombinant antibodies.

This is a *provisional* obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Given that USSN 08/791,391 appears to have the same inventive entity as the instant application, USSN 08/790,540 does not appear to have the same inventive entity; the following is noted.

Claims 56-59, 62, 65-68, 70-77, 84, 85, 90, 91 and 94-97 are directed to an invention not patentably distinct from claims 1-18 and 26-31 of copending application USSN 08/790,540.

Commonly assigned USSN 08/790,540, discussed above, would form the basis for a rejection of the noted claims under 35 U.S.C. § 103 if the commonly assigned case qualifies as prior art under 35 U.S.C. § 102(f) or (g) and the conflicting inventions were not commonly owned at the time the invention in this application was made. In order for the examiner to resolve this issue, the assignee is required under 37 C.F.R. § 1.78(c) to either show that the conflicting inventions were commonly owned at the time the invention in this application was made or to name the prior inventor of the conflicting subject matter. Failure to comply with this requirement will result in a holding of abandonment of the application. A showing that the inventions were commonly owned at the time the invention in this application was made will preclude a rejection under 35 U.S.C. § 103 based upon the commonly assigned case as a reference under 35 U.S.C. § 102(f) or (g).

Applicant's arguments, filed 1/22/01 (Paper No. 20), have been fully considered but are not found convincing essentially for the reasons set forth previously in Paper No. 16.

Applicant submits that the claimed enhanced LM609 grafted antibodies are patentably distinct from the claims in either of copending USSN 08/790,540 and 08,791,391, since the copending USSNs are not directed to an enhanced LM609 grafted antibody comprising one or more CDRs having at least one amino acid substitution in one or more CDRs of a LM609 grafted heavy chain variable region polypeptide.

As pointed out; for examination purposes and as applicant acknowledges; it appears that all that is required of the "enhanced" LM609 antibody is that the activity of the enhanced LM609 grafted antibody is maintained.

Therefore, the claimed "enhanced LM609 antibody" can have contrasting properties and still be considered enhanced with respect to the referenced LM609 antibody.

Therefore, the claimed recitation of "enhanced LM609 antibody" encompasses a variety of modified forms of the LM609, provided it differs from the native LM609 antibody and is held obvious over the copending claims drawn to humanized LM609 antibodies

Applicant's arguments are not found persuasive and the rejection is maintained.

14. No claim is allowed.

Claims 65, 72, 73, 77, 84, 85, 90, 91, 94-97 which recite specific amino SEQ ID NOS: 90 and 94 are considered free of the prior art, as the prior art does not appear to suggest these particular CDRs for LM609-specific recombinant antibodies.

While it is acknowledged that claims 60, 61, 63, 64, 69, 78-83, 92, 93 have been withdrawn from consideration by the examiner 37 CFR 1.142(b), as being drawn to a nonelected invention and/or species; a search has been conducted on the specific sequences set forth in SEQ ID NOS: 6, 8, 48, 50, 52, 54, 56, 58, 60, 62, 64, 68, 70, 72, 74, 76, 78, 80, 82, 84, 86, 88, 90, 92, 94, 96, 98 and 100.

These SEQ ID NOS. appear to be free of the prior art.

Applicant is invited to limit the claims to $\alpha v\beta 3$-specific antibodies which comprise these specific SEQ ID NOS, along with the appropriate structural and functional limitations.

15. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

16. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Phillip Gambel whose telephone number is (703) 308-3997. The examiner can normally be reached Monday through Thursday from 7:30 am to 6:00 pm. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christina Chan can be reached on (703) 308-3973. Any inquiry of a general nature or relating to the status of this application should be directed to the Technology Center 1600 receptionist whose telephone number is (703) 308-0196.

Papers related to this application may be submitted to Technology Center 1600 by facsimile transmission. Papers should be faxed to Technology Center 1600 via the PTO Fax Center located in Crystal Mall 1. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The CM1 Fax Center telephone number is (703) 305-3014.

Phillip Gambel, PhD.
Primary Examiner
Technology Center 1600
April 9, 2001

Phillip Gambel